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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/587,111	06/02/2000	Rory A.J. Curtis	MNI-062CP2DV1	6800

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EXAMINER	
ULM, JOHN D	

ART UNIT	PAPER NUMBER
1646	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/587,111	Applicant(s) Curtis
	Examiner John Ulm	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 12, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27, 29, 31-37, 39, 43-46, and 48* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27, 29, 31-37, 39, 43-46, and 48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1) Claims 27, 29, 31 to 37, 39, 43 to 46 and 48 are pending in the instant application. Claims 32, 35, 36, 43 to 46 and 48 have been amended and claims 28, 30, 31, 38, 40 to 42, 47 and 49 have been canceled as requested by Applicant in Paper Number 20, filed 12 May of 2003.

2) A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 May of 2003 has been entered.

3) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in line 14 on page 24. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01(p), which states that:

> "When a patent application with embedded hyperlinks and/or other forms of browser-executable code issues as a patent (or is published as a patent application publication) and the patent document is placed on the USPTO web page, when the patent document is retrieved and viewed via a web browser, the URL is interpreted as a valid HTML code and it becomes a live web link. When a user clicks on the link with a mouse, the user will be transferred to another web page identified by the URL, if it exists, which could be a commercial web site. USPTO policy does not permit the USPTO to

link to any commercial sites since the USPTO exercises no control over the organization, views or accuracy of the information contained on these outside sites. If hyperlinks and/or other forms of browser-executable code are embedded in the text of the patent application, examiners should object to the specification and indicate to applicants that the embedded hyperlinks and/or other forms of browser-executable code are impermissible and require deletion."

Correction is required.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6) Claims 27, 29, 31 to 37, 39, 43 to 46 and 48 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed specific and substantial credible utility. It has become clear from Applicant's arguments that the protein identified in the instant specification as hVR-2 does not bind capsaicin or any other specifically identified compound. Whereas the instant application has provided a description of an isolated DNA encoding an hVR-2 protein and the protein encoded thereby it does not disclose a specific biological role for this protein or its established significance to a particular disease, disorder of physiological process which one would wish to manipulate for a desired clinical effect. Given that the amino acid sequence of hVR-2 is only 41.3% identical to the known rat capsaicin VR-1 referred to in the declaration under 37 C.F.R. § 1.131 by Rory A. J. Curtis that was submitted on 12 May of 2003, one of ordinary skill would not conclude that these two different proteins bind the same ligand or spectrum of ligands. Further, given that VR-1 and VR-2 exhibit substantially different patterns of expression as described on page 63 of the instant specification, one would not

conclude that VR-2 mediates nociception simply because of its limited structural similarity to VR-1. It is clear from the instant specification that VR-2 appears to be an ion channel protein that is expressed in both the central and peripheral nervous systems. It is well known in the art that a substantial number of different ion channel proteins are expressed in the central and peripheral nervous systems, but all such ion channels are not believed to mediate nociception. Therefore, given the evidence of record one of ordinary skill would not believe that hVR-2 is a capsaicin receptor or that it mediates nociception.

It is clear from the instant specification that the receptor protein described therein as human vanilloid receptor (hVR)-2 is what is termed an "orphan receptor" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. Whereas one could readily employ a putative receptor protein of the instant invention in an assay to identify ligands thereto, as claimed, the information obtained thereby would be of little use until one discovers the identity of those physiological processes moderated by that putative receptor. Because the instant specification has failed to credibly identify a specific physiological process **which has been shown** to be influenced by the activation or inhibition of a putative receptor protein of the instant invention an artisan would have no way of predicting what effects the administration of that ligand to an organism would have. If one can not predict the effects that the administration of a ligand

of the putative receptor of the instant invention is going to have on an organism then it is unclear as to what practical benefit is derived by the public from the identification of that ligand by the claimed method.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", " [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", " [i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a method of identifying a compound which binds to a protein of as yet undetermined function or biological significance. There is absolutely no evidence of record or any line of reasoning that would support a conclusion the a protein of the instant invention is

associated in any way with the plurality of disorders that are listed in lines 11 to 20 on page 9 of the instant specification. Until some actual and specific significance can be attributed to the protein identified in the specification as hVR-2, or the gene encoding it, the instant invention is incomplete.

The protein employed in the binding assay of the instant invention is a compound known to be structurally analogous to proteins which are known in the art as ion channels or ionotropic receptors. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit or induce its activity is clearly to use it as the object of further research which has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for hVR-2 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

The disclosure in the instant specification that the hVR-2 protein described therein is structurally related to the capsaicin receptor VR-1 does not support a conclusion that hVR-2 will bind vanilloids and/or capsaicin. It is well known in the art that proteins belonging to the family of ionotropic receptors can be activated by a variety of compounds such as glutamate, glycine, acetylcholine and capsaicin, as well as other stimuli such as pH, voltage and ion differentials, heat and pressure. Because the differences between the amino acid sequence of the hVR-2 protein of the instant invention and that of hVR-1 are greater than the similarities, one would not conclude

that these two proteins respond to the same spectrum of stimuli or modulate the same cellular processes. It was well known in the art prior to the making of the instant invention that receptor proteins belonging to the same structural family, such as the G protein-coupled adrenergic and dopamine receptors, could share substantial amino acid sequence similarity and still modulate completely different physiological processes in response to structurally related but different ligands. The administration of dopamine to an individual certainly has a profoundly different effect than the administration of adrenaline, even though these two compounds are structurally related and the receptors for these two related compounds share substantial structural as well as amino acid sequence similarities. One would not reasonably conclude, based upon the limited amino acid sequence similarity between the hVR-2 protein of the instant invention and hVR-1 that the effects of clinical administration of an agonist or antagonist to one of these receptors would be predictive of the clinical effects of administering that agonist or antagonist to the other. Because one can not predict to which stimuli the instant receptor will respond by reviewing its amino acid sequence one can not conclude that hVR-2 will have the same utility as VR-1 simply because these two proteins share a limited degree of amino acid sequence similarity.

The text on pages 50 to 53 of the instant specification discloses that hVR-2 protein or the nucleic acid encoding it may serve as markers for chromosomal mapping, tissue typing and in forensic biology. The employment of a protein of the instant invention, a nucleic acid encoding that protein or a compound which binds to that protein as a chromosomal or tissue specific marker is not a substantial or specific utility. All cDNAs can be employed as chromosomal

markers. Further, all human proteins can invariably be classified into two categories, those which are expressed in a tissue or developmentally specific manner and those which are expressed ubiquitously. It can be alleged that any protein which is expressed in a tissue specific manner can be employed to detect the tissue in which it is expressed in a sample. Alternately, a human protein which is expressed ubiquitously can be employed to detect the presence of any human tissue in a sample. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

One could just as readily argue that any purified compound having a known structure could be employed as an analytical standard in such processes as nuclear magnetic resonance (NMR), infrared spectroscopy (IR), and mass spectroscopy as well as in polyacrylamide gel electrophoresis (PAGE), high performance liquid chromatography (HPLC) and gas chromatography. None of these processes could be practiced without either calibration standards having known molecular structures or, at least, a range of molecular weight markers having known molecular weights. One could further extrapolate upon this premise by asserting that any item having a fixed measurable parameter can be employed to calibrate any machine or process which measures that parameter. For example, any item having a constant mass within an acceptable range can be employed to calibrate a produce scale in a grocery store. The calibration of produce scales is certainly an important function since most states require produce scales to be calibrated and certified. Therefore, to accept Applicant's arguments that any nucleic acid

encoding any protein of human origin is useful as a marker would be comparable to conceding that any object of fixed mass has *prima facie* utility as a weight standard, irrespective of any other properties possessed by that object. It was just such applications that the court appeared to be referring to when it expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation (*Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966)). Because the steroid compound which was the subject of that decision had a known structure and molecular weight it could have readily been employed as a molecular standard at that time. Further, because that compound was a hydrocarbon it certainly could have been employed in the well known process of combustion for purposes of lighting and/ or the generation of heat. The generation of heat by combustion of hydrocarbons certainly was and remains an important process. Irrespective of such obvious utilities, the court still held that the compound produced by the process at issue in *Brenner v. Manson* did not have a specific and substantial utility.

To grant Applicant a patent encompassing a binding assay employing a naturally occurring human protein of as yet undetermined biological significance would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *(Brenner v. Manson, Ibid)*. To grant Applicant a patent on the claimed assay based upon an assertion that a compound identified thereby can be employed as a tissue marker is clearly

prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted and would be no different than granting a patent on the process disputed in *Brenner v. Manson* on the premise that the steroid produced thereby was useful as an analytical standard or as a combustible fuel source.

7) Claims 27, 29, 31 to 37, 39, 43 to 46 and 48 are rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101.

8) Claims 43 to 46 and 48 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while providing the guidance needed to practice a method of identifying a ligand which binds to a receptor protein comprising the amino acid sequence presented in SEQ ID NO:5 of the instant specification, does not reasonably provide the guidance needed to practice a binding assay which employs a protein having anything less than the entire amino acid sequence presented in SEQ ID NO:5 for those reasons of record as applied to claims 31 to 36, 41 to 46 and 48 in section 6 of Paper Number 18. Applicant's arguments in traversal of this rejection essentially repeat those arguments of record which have been answered on the record.

The example from the *Revised Interim Written Description Guidelines Training Materials* which Applicant has relied upon in traversal of this rejection is not analogous. An enzyme has utility so long as it has a catalytic activity. This is not true of a protein of the instant invention. As disclosed in the text at the top of page 3 of the instant specification, a protein of the instant invention is potentially useful in the identification of agonists and antagonists thereto because such

agonist or antagonists might be useful in pain management in a clinical environment. It is not sufficient that a protein employed in this capacity simply function as a vanilloid-gated ion channel. As stated in the original rejection, it is essential to the practice of the claimed method that the protein employed therein provide an authentic response to a test compound wherein that response is predictive of how the natural protein will respond to that compound *in vivo*. As stated in the original rejection, in the absence of both working examples of intentionally altered VR-2 proteins and information on the ligand and signaling pathway of the disclosed protein an artisan could not alter a single amino acid residue in SEQ ID NO:5 with any confidence that the resulting protein will function in a manner that is representative of its native analog and the instant specification does not disclose how to use information that is obtained from an assay which employs a protein that does not function in a manner that is representative of its native analog.

This rejection is not in conflict with the rejection of the instant claims for lack of utility. The instant claims are drawn to a binding assay. The binding assay lacks utility because the information obtained therefrom has no immediate practical and specific application. The indication that hVR-2 may be involved in nociception does not provide a specific utility for the claimed invention in its currently available form because further experimentation is required to identify a specific practical utility for that invention, and the law precludes the need for any experimentation for the purpose of establishing a utility for an invention. Further, the only utility **disclosed** in the instant specification for the information derived from the claimed assay relates to the native protein and the instant specification does not provide the guidance needed to

predictably alter hVR-2 with any reasonable expectation that the resulting protein will retain the ability to produce an authentic response.

9) The declaration by Rory A. J. Curtis filed on 12 May of 2003 under 37 CFR 1.131 is sufficient to overcome the Julius et al. reference.

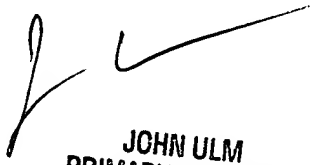
10) Applicant's arguments filed 12 May of 2003 have been fully considered but they are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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